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Birth seasonality studies in a large Prader–Willi syndrome cohort

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Abstract

Prader-Willi syndrome (PWS) is generally due to sporadic paternal deletions of the chromosome 15q11-q13 region followed by maternal disomy 15. Advanced maternal age is more commonly seen in those with maternal disomy 15. Environmental factors (e.g., drug use, occupational chemical exposure, infectious agents, and irradiation) could account for chromosome changes. Previous evidence of differences in male and female gametogenesis could suggest an environmental role in the causation of the paternal 15q11-q13 deletion seen in PWS. Certain occupations such as hydrocarbon-exposing occupations (e.g., landscaping, farming, and painting) and viral exposure (e.g., human coronavirus 229E causing upper respiratory infections in adults with an incorporation site in the human genome at chromosome 15q11) can be seasonal in nature and contribute to chromosome damage. To assess, we reviewed birth seasonality data in a large cohort of individuals with PWS recruited nationally (N = 355) but no significant differences were seen by month between those with the 15q11-q13 deletion compared with maternal disomy 15 when analyzing quarterly seasonal patterns. Although early evidence supported birth seasonality differences in PWS, a larger number of individuals in our recent study using advanced genetic testing methods did not find this observation.

KEYWORDS

birth seasonality, environmental factors, Prader–Willi syndrome (PWS), PWS genetic subtypes

Prader–Willi syndrome is a genetically imprinted disorder due to a paternal deletion of the chromosome 15q11-q13 region in the majority of cases. PWS is most often sporadic in occurrence and characterized by infantile hypotonia, a poor suck reflex with feeding difficulties, hypogonadism and hypogenitalism, growth and other hormone deficiencies with short stature, hyperphagia with early childhood obesity, mental deficiency and behavioral problems (Butler, 2016; Butler, Lee, & Whitman, 2006; Cassidy, Schwartz, Miller, & Driscoll, 2012). The chromosome 15q11-q13 deletion is seen in about 60% of those with PWS, maternal disomy (UPD) 15 or both chromosome 15 s inherited from the mother in 35% while the remaining individuals have an imprinting defect involving the imprinting center on

chromosome 15 which regulates the activity of imprinted genes or from chromosome 15 rearrangements (e.g., translocations, inversions) (Butler et al., 2019).

Previous studies have suggested an environmental role for causing the paternal 15q11-q13 deletion seen in PWS (Strakowski & Butler, 1987) and influenced by differences in male and female gametogenesis. Environmental factors can cause chromosome damage and abnormalities while advanced maternal age is more commonly seen in those with maternal disomy 15 (Butler et al., 2019). In female meiosis, the germ cells are arrested in the dictyotene stage of meiosis I during fetal life and a lengthy duration exists until the time of ovulation. This arrested stage could also be influenced by the environment impacting chromosome nondisjunction leading to maternal disomy 15 (e.g., Butler et al., 2009).

Proliferation of germ cells in males is continuous and DNA replication could be sensitive to environmental effects with an increased risk for chromosomal deletions involving breakage and reunion. Environmental factors influencing paternal gametogenesis could include drug use, occupational exposure, infectious agents and irradiation leading to chromosome damage (Akefeldt, Anvret, Grandell, Nordlinder, & Gillberg, 1995; Cassidy, Gainey, & Butler, 1989; Strakowski & Butler, 1987). Increased incidence of periconceptional employment in hydrocarbon-exposing occupations in fathers of children with PWS was reported by Strakowski and Butler (1987) supported by other studies with paternal exposure to gasoline/petrol (Akefeldt et al., 1995). Certain occupations may also represent seasonal changes such as hydrocarbon-exposing occupations (e.g., landscaping, farming, painting; Bauchinger, Dresp, Schmid, & Hauf, 1982; Haglund, Lundberg, & Zech, 1980; Kucerová, Polívková, & Bátora, 1979; Strakowski & Butler, 1987). Furthermore, infectious agents such as influenza viruses are seasonal including the human coronavirus 229E causing upper respiratory infections in adults. This virus has an incorporation site in the human genome at chromosome 15q11 allowing this virus to be absorbed to and received within the host cell (Sakaguchi & Shows, 1982) and could influence DNA replication causing chromosome damage during male meiosis.

To investigate whether children with PWS having the 15q11-q13 deletion versus non-deletion status showed differences in birth months, Butler, Ledbetter, and Mascarello (1985) analyzed birth seasonality data from three separate medical centers in the USA and examined monthly variation from grouped PWS data according to their chromosome 15 status. This study was done prior to identification of maternal disomy 15 or imprinting defects causing PWS in those without the chromosome 15q11-q13 deletion (e.g., Nicholls, Knoll, Butler, Karam, & Lalande, 1989). A significant difference was found in the 124 patients with PWS studied in 1985 and 46% with chromosome 15q11-q13 deletions were born in the fall months (September, October, November) while only 7% were born in the winter (December, January, February). Those with PWS and the non-deletion status, now recognized as having maternal disomy 15 in the vast majority of cases without the deletion, were nearly equally distributed among the four seasons. These birth seasonality findings showed an over-representation of deliveries in the fall with under-representation in the winter months supporting a possible environmental influence, seasonal in nature (e.g., December, January, February) on male meiosis prior to conception during sperm development and maturation impacting chromosome 15. The winter month observation data agreed with the time of increased seasonal infections during this time including upper respiratory influenza exposure in the father periconceptionally.

Two other reports have examined birth seasonality in PWS, one study from Korea involving 211 patients (Yang et al., 2015) and the second study from Japan involving 271 subjects (Ayabe et al., 2013). In the Korean study, more PWS babies were born with the deletion in January compared to other months and more babies with UPD were born in the spring. September and October showed the highest number of births in the deletion group in the Japanese study while November showed the highest number of births in the UPD group. There was no statistical significance in seasonal variation in births of the 211 patients with PWS in the Korean population but a significant difference was found in monthly variation between PWS with the deletion and the general population. Ayabe et al. (2013) found a seasonal variation in the number of subjects in the deletion group with approximately 35% of the Japanese patients born in the autumn months while only 18% were born in the spring. The number of Japanese births in the UPD group and the general population was nearly equal in distribution among the four seasons.

The rationale for our study was to again examine birth seasonality data from a PWS cohort of 355 individuals (197 F; 158 M; average age ± *SD* = 13.4 + 12.0 years) which was three times larger than the PWS birth seasonality dataset reported earlier in the US population in 1985 (Butler et al., 1985). Our larger PWS cohort consisted of 217 individuals with the chromosome 15q11-q13 deletion, 127 individuals with maternal disomy 15 and an imprinting defect in 11 subjects recruited for a nationwide natural history study (Butler et al., 2018, 2019). Twenty-two percent of the individuals with PWS recruited nationally at four different sites (California, Kansas, Tennessee, and Florida) were less than 21 years of age and predominantly Caucasian (93%). In review of birth seasonality data from 344 individuals from the PWS cohort (excluding 11 individuals with PWS and imprinting defects), no significant differences were seen by month between those with the deletion versus maternal disomy 15 or by quarterly seasonal assessments using chi-square (X^2) analysis (Figure 1; Table 1). However, February showed the second to highest number of births in the deletion subtype group and the lowest number for maternal disomy 15. The number of births observed in the fall months (N = 22) were less than one-half the number of births observed in the spring months (N = 45) while the number of births observed in the deletion group was similar in all four seasons. Potential environmental factors could play a role with contributions of age as older mothers are over-represented in those families with PWS children having maternal disomy 15 due to non-disjunction (Butler et al., 2019). The maturation of sperm occurs in fathers ~2 months prior to conception and may be impacted by seasonal factors (e.g., viruses) or by inhibiting chromosome 15 nondisjunction events in female gametogenesis, particularly in meiosis I (Butler et al., 2009).

Advanced maternal age and chromosome nondisjunction are reported in other numerical chromosome disorders such as Down syndrome (Jongbloet, 1971; Lam & Miron, 1987). Monthly variation in

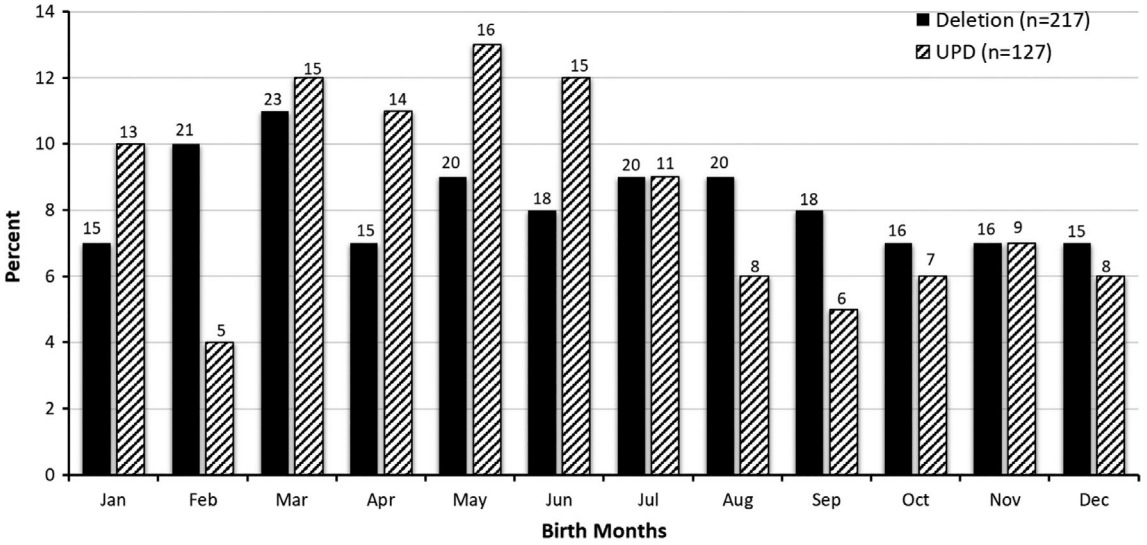

FIGURE 1 Birth month data from 344 individuals with Prader–Willi syndrome with 15q11-q13 deletion (*N* = 217) or non-deletion maternal disomy 15 (UPD; *N* = 127) status. The percentage and the number of births per month represented by the number at the top of each bar for the deletion and maternal disomy 15 subject groups. Fewer babies with PWS and maternal disomy 15 were born in the month of February compared with the deletion group but not overall significantly different (X^2 ~11.0; p = .443)

TABLE 1 Birth seasonality data for individuals with Prader–Willi syndrome

Subject group	Fall	Winter	Spring	Summer	χ^2 (p)
Deletion (*N* = 217)	50 (23.0%)	51 (23.5%)	58 (26.7%)	58 (26.7%)	3.61 (0.307)
UPD (*N* = 127)	22 (17.3%)	26 (20.5%)	45 (35.4%)	34 (26.8%)	

the incidence of birth of patients with Down, Turner, and Klinefelter syndromes has also been reported with a significant increase in the frequency of conceptions for Down syndrome during the first 4 months of the year (Jongbloet, 1971; Videbech & Nielsen, 1984). Seasonal variation in hormone production by hypothalamus-pituitary-ovarian axis has been suggested to lead to seasonality in conception rates of Down syndrome and errors in nondisjunction (Stolwijk, Jongbloet, Zielhuis, & Gabreëls, 1997) and could impact PWS, as well. The underlying mechanism for the higher prevelance of Down syndrome with advanced maternal age is not clear. A common hypothesis includes aging of the ovum or hormonal imbalance causing suboptimal microvasculature to develop around the maturing follicles with oxygen deficiency leading to smaller sized spindles followed by displacement and nondisjunction of chromosomes (Gaulden, 1992; Jongbloet, 1975; Polani, Briggs, Ford, Clarke, & Berg, 1960; Stolwijk et al., 1997). Seasonal variation in human reproduction including ovulation, sperm production, and births has also been observed and will require more study to identify ongoing environmental factors (Lam & Miron, 1987; Levine, 1994; Roenneberg & Aschoff, 1990).

In summary, birth seasonality differences in PWS were reported in the US population over three decades ago prior to current genetic testing and PWS methylation status but not identified in a larger number of individuals with genetically confirmed PWS that we collected nationally in the US using advanced testing for accurate determination of the 15q11-q13 deletion and maternal disomy 15 status. Our recent study did not support an earlier observation in 1985 of those with PWS and the 15q11-q13 deletion born more frequently in the fall months but seasonality was seen in a different PWS cohort from Japan. Further investigations are needed as to whether environmental factors could contribute to chromosome 15 defects and/or chromosomal nondisjunction events in PWS. Similar investigations which are beyond the scope of this report could be undertaken and encouraged in Angelman syndrome, a second genomic imprinting disorder involving the same chromosome 15q11-q13 deletion but of maternal origin, paternal disomy 15, chromosome 15 imprinting defects, or *UBE3A* gene mutations (Dagli, Buiting, & Williams, 2012). A comparison of an Angelman syndrome dataset may be fruitful to further address birth seasonality in imprinted disorders including a lower number of births in the month of February seen in PWS with maternal disomy 15 but not reaching a level of significance.

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CONFLICT OF INTEREST

None.

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